Published in final edited form as:

Am J Med Genet A. 2017 June ; 173(6): 1656–1662. doi:10.1002/ajmg.a.38171.

***de Novo* Unbalanced Translocation (4p duplication/8p deletion) in a Patient with Autism, OCD, and Overgrowth Syndrome**

Angela Sagar^{1,2}, Dalila Pinto^{3,4}, Fedra Najjar², Stephen J. Guter², Carol Macmillan⁵, and Edwin H. Cook²

¹Division of Psychiatry and Behavioral Sciences, Children's National Medical Center, Washington, District of Columbia

²Institute for Juvenile Research, Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois

³The Centre for Applied Genomics, The Hospital for Sick Children, Toronto, Ontario, Canada

⁴Departments of Psychiatry, and Genetics and Genomic Sciences, Seaver Autism Center, The Mindich Child Health & Development Institute, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA

⁵Department of Pediatrics, University of Chicago, Chicago, Illinois

Abstract

Chromosomal abnormalities, such as unbalanced translocations and copy number variants (CNVs), are found in autism spectrum disorders (ASDs) [Sanders et al., 2011]. Many chromosomal abnormalities, including submicroscopic genomic deletions and duplications, are missed by G-banded karyotyping or Fragile X screening alone and are picked up by chromosomal microarrays [Shen et al., 2010]. Translocations involving chromosomes 4 and 8 are possibly the second most frequent translocation in humans and are often undetected in routine cytogenetics [Giglio et al., 2002]. Deletions of 4p16 have been associated with Wolf-Hirschhorn syndrome while 4p16 duplications have been associated with an overgrowth syndrome and mild to moderate mental retardation [Partington et al., 1997]. The 8p23.3 region contains the autism candidate gene *DLGAP2*, which can contribute to autism when disrupted [Marshall et al., 2008]. There has been a case report of a family with autism spectrum disorder (ASD), prominent obsessional behavior, and overgrowth in patients with der (8) t (4;8) p (16;23) [Partington et al., 1997]. This is an independent report of a male patient with autism, obsessive compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), and an overgrowth syndrome, whose *de novo* unbalanced translocation der (8) t (4;8) p (16.1→ter ; 23.1→ter) was initially missed by routine cytogenetics but detected with SNP microarray, allowing higher resolution of translocation breakpoints.

Keywords

Autism; der(8) t(4; 8); 8p deletion; 4p duplication; Overgrowth Syndrome; Obsessive Compulsive Disorder; ADHD

Introduction

The autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders characterized by persistent impairment in reciprocal social communication and social interaction as well as the presence of restricted, repetitive patterns of behavior, interests, or activities; these symptoms are present from early childhood and limit or impair everyday functioning [American Psychiatric Association, 2013]. Autism is known to be strongly heritable [Bailey et al., 1995; Klei et al., 2012; Stilp et al., 2010] with environmental influences [Hallmayer et al., 2011]. Mode of inheritance can play a significant role in the genetic acquisition of autism as evidenced by imprinting of 15q11 – q13 leading to autism or atypical autism when maternally inherited but not when paternally inherited [Cook et al., 1997]. Pinto and colleagues [2010] found that many autism cases carried a higher global burden of rare (less than 1%) genic copy number variants (CNVs) when compared to controls, adding to the body of evidence that multiple rare CNVs contribute to vulnerability to ASDs [Cook and Scherer, 2008; Pinto et al., 2014].

We describe here a patient with autism, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and an overgrowth syndrome, who had an unbalanced translocation der(8) t(4;8)(p16.1→pter ; p23.1→pter) identified during a larger Autism Genome Project SNP microarray CNV study [Pinto and others 2014], which was here confirmed to be *de novo* by FISH and microsatellite studies.

Clinical report

The patient was born at term to nonconsanguineous healthy parents after a pregnancy complicated by preterm labor treated with cervical cerclage, bedrest from month 5 and terbutaline. He was noted in the perinatal period to be very irritable. Birth weight was 2.55 kg (5th centile), birth length was 50.8 cm (50th centile)[Hall et al., 2006].

He was initially diagnosed with ADHD and learning disability, enrolled in early childhood services, and received speech, language, and occupational therapy at the age of 3 years. At 5 years of age he was placed in a special education school; he was seen by neurology and he was diagnosed with autism by a psychiatrist.

At age 12 years he was enrolled in an escitalopram pharmacogenetic study at the University of Chicago according to a protocol approved by the University of Chicago IRB and subsequently the University of Illinois at Chicago IRB [Owley et al., 2010]. He was clinically diagnosed with autism; the Autism Diagnostic Observation Schedule (ADOS) [Lord et al., 2002] and the Autism Diagnostic Interview – Revised (ADI-R)[Rutter et al., 2003] were administered with a classification of autism. The Raven's Coloured Progressive Matrices (RCPM)[Raven, 1993] was administered to measure nonverbal intelligence (standard score 33) and the Peabody Picture Vocabulary Test, Third Edition (PPVT-III) [Dunn and Dunn, 1997] was administered to assess receptive language; he achieved an age equivalent (AE) of 4 years, 3 months.

During the course of the trial, he was unable to tolerate an upward titration of escitalopram beyond the starting dose of 2.5mg each day. He had an improvement in Aberrant Behavior Checklist – Community, Irritability subscale (ABC-IRR)[Aman et al., 1995; Aman et al., 1985] from a baseline score of 12 to a score of 4 after one week of being on 2.5mg each day of escitalopram. Titration up to 5mg each day on week two of the study led to an exacerbation to an ABC-IRR of 22 so his dose was reduced to 2.5mg each day. At the conclusion of the trial at week 11, his ABC-IRR score was 1.

At age 18, he returned to the University of Illinois at Chicago to participate in The Autism Simplex Collection (TASC). Adaptive skills were evaluated by the Vineland Adaptive Behavior Scales, Second Edition (VABS II)[Sparrow et al., 2005] on which he received an Adaptive Behavior Composite standard score of 53. He was administered the Peabody Picture Vocabulary Test, Fourth Edition (PPVT 4)[Dunn and Dunn, 2007] at this time as well and his AE was 5 years, 5 months. His total score on the Repetitive Behavior Scale-Revised (RBS-R)[Bodfish et al., 1999; Lam and Aman, 2007] was 16 and his total number of items endorsed was 16. The Social Responsiveness Scale (SRS)[Constantino et al., 2004] was administered and his *T*-Score was 86, in the severe range. His ABC-IRR score was 5.

His OCD symptoms consisted of excessive hand washing, excessive use of toilet paper, paper towels, and other repetitive behaviors. Our patient also suffered from poor sleep, irritability, and aggression – symptoms related to his OCD and related anxiety. Clonidine helped with sleep, Adderall helped with hyperactivity, inattention, and irritability. However, treating the anxiety and OCD and adjusting the SSRI dose remained a challenge.

When he was 22 years-old, medications were adjusted to target OCD and skin picking. Escitalopram was increased from 5 to 10 mg; Adderall was decreased from a total of 40 mg to 20 mg in divided doses, and risperidone was added. Between the age of 22 and 25 his Adderall and risperidone doses remained unchanged. His anxiety improved with gradual increases to his escitalopram dose from 10mg to 20 mg a day. He was better able to use sentences to communicate and he was more comfortable making brief eye contact when encouraged. His skin healed, indicating a decrease in skin picking. His other OCD-related behaviors also improved and he was more receptive to attending an adult program regularly on this medication regimen.

Additional past medical history included a ventricular septal defect that closed spontaneously in infancy. He had eczema as a child and psoriasis as an adult. He had headaches treated effectively with an over-the-counter preparation. He was otherwise healthy with no hospital admissions and no history of surgery. Family history revealed that his 7 years older sister and 18 months older brother developed typically. There was no family history of OCD or pervasive developmental disorder, although his mother reported that father's family had difficulty with socialization.

Physical Examination at 21 Years Old

On examination, he was macrocephalic (head circumference 60 cm, 1.5 cm greater than the 98th centile). Weight was 102.5 kg (1.5 kg greater than the 97th centile) and height was 183 cm (81st centile) with a body mass index of 30.6 (95th centile)[Hall et al., 2006]. His head

was scaphocephalic, and he had hypertrichosis of the eyelashes. He had an extra fold in the cartilage at the superior aspect of each pinna, and had a prominent lower lip. His left upper canine tooth was congenitally absent, and his mother reported that his dentist noted a duplicate set of wisdom teeth in his lower jaw. He had a mild thoracic scoliosis concave to the right, and 2 lacy hyperpigmented macules: 6×1.5 cm on the left flank, and 5×2 cm on the right elbow. He had mild global hypotonia and preferred to walk on his toes, but did not have Achilles tendon contractures, muscle weakness or spasticity. Cranial nerve, coordination and sensory examinations were normal.

Additional measurements were obtained he was 26 years-old. See Supplementary Information (Table IS) for these measurements and a summary of the clinical findings.

Microarray Analysis and CNV Validation

Earlier fragile X testing and initial routine Giemsa-banded (G-banded) karyotyping for the patient were negative before presentation to our clinic. As part of the IRB approved TASC study [Buxbaum et al., 2014], DNA was extracted from whole-blood for the patient and both parents, hybridized to the Illumina 1M duo DNA Beadchip array (Illumina Inc., San Diego, CA, USA), and analyzed for CNV as previously described. Validation of the $\sim 9\text{Mb}$ -4p16.3 duplication and $\sim 7\text{Mb}$ -8p21.3 deletion was performed with SYBR Green I-based real-time (RT) quantitative PCR (qPCR) using the standard curve method [Pinto et al., 2010].

Materials and Methods

Sequential G-to-FISH

Freshly drawn blood from patient, both parents, and unaffected male older sibling was obtained for subsequent FISH and microsatellite analyses. Metaphase slides were obtained from peripheral blood lymphocytes and conventional G-banded karyotype was performed for all samples. No 4p/8p abnormalities were apparent in parents or sibling. Three-color FISH was performed using standard procedures with RP11 clones. Probe and slide preparation as well as DNA hybridization followed conventional methods [Joseph-George et al., 2011]. FISH analysis was conducted on both metaphase and interphase chromosomes.

Microsatellite Testing

The DNA from the case subject and all family members was extracted from blood in EDTA using standard methods. Paternity testing used the AmpFISTR® Identifiler® PCR Amplification Kit. Informative array SNP and microsatellite marker analyses were conducted to determine the chromosome origin for the 8p16.3-pter deletion and 4p16.3-pter duplication.

Genetic Results

A relatively large ($\sim 6,839,842$ bp) deletion of 8p and a duplication of $\sim 8,962,937$ bp of 4p were found from the CNV analysis previously reported in a table in Pinto et al 2014 [2014]. 8p23.2 was deleted from the p telomere to hg18 chr:6994825 8p(23.1 $\rightarrow$ ter). 4p16.1 was duplicated from the 4p telomere to chr4:9016339 or 4p(16.1 $\rightarrow$ ter).

FISH confirmed our patient's *de novo* der(8) t(4;8)(p16.1→pter ; p23.1→pter) unbalanced translocation (Figure 1). Informative PCR markers demonstrated that both the *de novo* 8p deletion and 4p duplication occurred on the maternal chromosome (Figure 2 and Figure 3). He did not show mosaicism – at least 100 interphase nuclei and 21 metaphases were inspected, and all of his cells showed the unbalanced t(4;8).

Discussion

A patient with autism, OCD, ADHD, and an overgrowth syndrome was found to have a *de novo* unbalanced translocation with a 4p duplication and an 8p deletion: der (8) t (4;8) p (16.1→ter ; 23.1→ter). Informative markers demonstrated that the 8p deletion and 4 p duplication occurred on the maternal chromosome.

Partington et al [1997] reported a family with der(8) t(4;8) p(16.2;23.1) mat. A male had obsessional behavior, overgrowth, and IQ of 50, and was diagnosed with Asperger's disorder (currently defined as autism spectrum disorder). His full sister also had overgrowth, less severe obsessional behavior, and an IQ of 54. The first cousin with the same translocation had overgrowth and an IQ of 65, but the presence or absence of obsessional behavior was not documented. Our patient's 4p partial trisomy contributed to his overgrowth syndrome [Giglio et al., 2002; Partington et al., 1997; Tranebjaerg et al., 1984]. *FGFR3* was likely present in 3 copies and caused him to present clinically with large hands and feet. Cyr and colleagues reported on a 4p16.3 microduplication involving *FGFR3* in a male who was last seen at age 2 years; overgrowth was not reported and this may be because the patient was too young to exhibit this feature of 3 copies of *FGFR3* [Cyr et al., 2011]. It is possible that our patient's 4p16.2 duplication contributed to his autism; this region is large enough that other genes may contribute but Partington reported other translocations that did not involve 8p and did not report ASD, so 4p duplications in that series were associated with overgrowth but not reported ASD. In summary, although exclusion of other causes of overgrowth was not performed, overgrowth has been a consistent finding in 4p partial trisomy.

Recently, Skrlec and colleagues described a 5month-old patient who had been referred to genetics because of dysmorphic features including a narrow forehead, hirsutism, wide nasal bridge, anteverted nostrils, low set and malformed ears, small mandible, and low hairline on the neck; he also had an atrio-ventricular septal defect [2014]. His *de novo* translocation was determined using G-banding and FISH. G-banding demonstrated an unbalanced karyotype with extra chromosomal material at the short arm of chromosome 8 and deletion of the 8 p subtelomeric probe, D8S504. A total of 3 hybridization signals for the probe WHCR (4p16.3) were visualized – 2 on each of the 4p arms and one signal at the p arm of the derivative chromosome 8. The patient Skrlec and colleagues described did not have chromosomal microarray (CMA) performed, making it difficult to clearly define the similarities with our patient's translocation.

Der (8) t (4;8) (p16;p23) has been considered to possibly be the second most frequent translocation after t(11q;22q) in humans; many of these translocations may not be detected by routine cytogenetics [Giglio et al., 2002]. However, there have been few reports of der (8) t(4;8) p(16;23) providing details including behavioral phenotype.

8p23 deletions have been associated with mild mental retardation, cardiac abnormalities, microcephaly, and autism [Giglio et al., 2000; Hutchinson et al., 1992; Tranebjaerg et al., 1984]. A duplication at 8p23.2 that intersected and likely disrupted *DLGAP2* has been associated with a male with ASD, repetitive behaviors, and moderate receptive/expressive language delay – discussed by both Marshall in 2008 and, after analysis on a higher-resolution array, reported by Pinto and colleagues [Marshall et al., 2008; Pinto et al., 2010]. The *DLGAP* family of proteins interacts with SHANK scaffolding proteins, which are involved in the assembly and stability of synapses [Romorini et al., 2004]. Some SHANK proteins are organizers of post synaptic density [Romorini et al., 2004]. Because disruptions of *SHANK3* and of *DLGAP2* have been associated with ASD [Durand et al., 2007; Gau et al., 2010], it is possible that a deletion of *DLGAP2* contributed to our patient's autism [Pinto et al., 2010; Romorini et al., 2004]. It is also of note that *Dlgap3* (*Sapap3*) knockout mice have prominent compulsive behavior [Welch et al., 2007] and that rare variants of *DLGAP3* have been identified in patients with OCD [Zuchner et al., 2009].

4p and 8p deletions are not easily detected in routine cytogenetics, and many authors mention how they were missed initially [Giglio et al., 2002; Partington et al., 1997; Tranebjaerg et al., 1984]. This was true with our patient as well, whose translocation was eventually detected by CMA. This further supports the argument that CMA should be used in the diagnostic testing of patients with ASD [Shen et al., 2010].

In conclusion, we report the detailed phenotype of the second case of der (8) t (4;8) p (16;23) with ASD and prominent OCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the patient and his family for their cooperation, assistance, and support in this project. Funding was provided in part by an Autism Center of Excellence award from NICHD (P50 HD055751) and NIMH 5T32MH067631 Training in the Neuroscience of Mental Health.

References

- Aman MG, Burrow WH, Wolford PL. The Aberrant Behavior Checklist-Community: factor validity and effect of subject variables for adults in group homes. *Am J Ment Retard.* 1995; 100(3):283–292. [PubMed: 8554775]
- Aman MG, Singh NN, Stewart AW, Field CJ. The Aberrant Behavior Checklist: a behavior rating scale for the assessment of treatment effects. *Am J Ment Defic.* 1985; 89(5):485–491. [PubMed: 3993694]
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th. Washington, DC: American Psychiatric Association; 2013.
- Bailey A, Lecouteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. Autism as a strongly genetic disorder - Evidence from a British twin study. *Psychol Med.* 1995; 25(1):63–77. [PubMed: 7792363]
- Bodfish JW, Symons FJ, Lewis MH. *The Repetitive Behavior Scale.* Western Carolina Center Research Reports. 1999

- Buxbaum JD, Bolshakova N, Brownfeld JM, Anney RJ, Bender P, Bernier R, Cook EH, Coon H, Cuccaro M, Freitag CM, Hallmayer J, Geschwind D, Klauck SM, Nurnberger JI, Oliveira G, Pinto D, Poustka F, Scherer SW, Shih A, Sutcliffe JS, Szatmari P, Vicente AM, Vieland V, Gallagher L. The Autism Simplex Collection: an international, expertly phenotyped autism sample for genetic and phenotypic analyses. *Mol Autism*. 2014; 5:34. [PubMed: 25392729]
- Constantino JN, Gruber CP, Davis S, Hayes S, Passanante N, Przybeck T. The factor structure of autistic traits. *J Child Psychol Psychiatry*. 2004; 45(4):719–726. [PubMed: 15056304]
- Cook EH Jr, Lindgren V, Leventhal BL, Courchesne R, Lincoln A, Shulman C, Lord C, Courchesne E. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am J Hum Genet*. 1997; 60(4):928–934. [PubMed: 9106540]
- Cook EH Jr, Scherer SW. Copy-number variations associated with neuropsychiatric conditions. *Nature*. 2008; 455(7215):919–923. [PubMed: 18923514]
- Cyr AB, Nimmakayalu M, Longmuir SQ, Patil SR, Keppler-Noreuil KM, Shchelochkov OA. A novel 4p16.3 microduplication distal to WHSC1 and WHSC2 characterized by oligonucleotide array with new phenotypic features. *Am J Med Genet A*. 2011; 155A(9):2224–2228. [PubMed: 21815251]
- Dunn, LM., Dunn, DM. Peabody Picture Vocabulary Test—Fourth Edition. Minneapolis MN: Pearson; 2007.
- Dunn, LM., Dunn, LM. Peabody Picture Vocabulary Test—Third Edition. Circle Pines, MN: American Guidance Service; 1997.
- Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Gillberg IC, Anckarsater H, Sponheim E, Goubran-Botros H, Delorme R, Chabane N, Mouren-Simeoni MC, de Mas P, Bieth E, Roge B, Heron D, Burglen L, Gillberg C, Leboyer M, Bourgeron T. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet*. 2007; 39(1):25–27. [PubMed: 17173049]
- Gau SSF, Chien WH, Wu YY, Huang YS, Fang JS, Chen YJ, Soong WT, Chiu YN, Chen CH. Identification and molecular characterization of two novel chromosomal deletions associated with autism. *Clin Genet*. 2010; 78(5):449–456. [PubMed: 20236125]
- Giglio S, Calvari V, Gregato G, Gimelli G, Camanini S, Giorda R, Ragusa A, Gueneri S, Selicorni A, Stumm M, Tonnies H, Ventura M, Zollino M, Neri G, Barber J, Wiczorek D, Rocchi M, Zuffardi O. Heterozygous submicroscopic inversions involving olfactory receptor-gene clusters mediate the recurrent t(4;8)(p16;p23) translocation. *Am J Hum Genet*. 2002; 71(2):276–285. [PubMed: 12058347]
- Giglio S, Graw SL, Gimelli G, Pirola B, Varone P, Voullaire L, Lerzo F, Rossi E, Dellavecchia C, Bonaglia MC, Digilio MC, Giannotti A, Marino B, Carrozzo R, Korenberg JR, Danesino C, Sujansky E, Dallapiccola B, Zuffardi O. Deletion of a 5-cM region at chromosome 8p23 is associated with a spectrum of congenital heart defects. *Circulation*. 2000; 102(4):432–437. [PubMed: 10908216]
- Hall, JG., Allanson, JE., Gripp, KW., Slavotinek, AM. Handbook of physical measurements. 2nd. Oxford; New York: Oxford University Press; 2006.
- Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, Miller J, Fedele A, Collins J, Smith K, Lotspeich L, Croen LA, Ozonoff S, Lajonchere C, Grether JK, Risch N. Genetic heritability and shared environmental factors among twin pairs with autism. *Arch Gen Psychiatry*. 2011; 68(11):1095–1102. [PubMed: 21727249]
- Hutchinson R, Wilson M, Voullaire L. Distal 8p deletion (8p23.1----8pter): a common deletion? *J Med Genet*. 1992; 29(6):407–411. [PubMed: 1619636]
- Joseph-George AM, He Y, Marshall CR, Wong RC, MacDonald JR, Fahey CA, Chitayat D, Chun K, Ryan G, Summers AM, Winsor EJ, Scherer SW. Euchromatic 9q13-q21 duplication variants are tandem segmental amplifications of sequence reciprocal to 9q13-q21 deletions. *J Med Genet*. 2011; 48(5):317–322. [PubMed: 21429932]
- Klei L, Sanders SJ, Murtha MT, Hus V, Lowe JK, Willsey AJ, Moreno-De-Luca D, Yu TW, Fombonne E, Geschwind D, Grice DE, Ledbetter DH, Lord C, Mane SM, Martin CL, Martin DM, Morrow EM, Walsh CA, Melhem NM, Chaste P, Sutcliffe JS, State MW, Cook EH, Roeder K, Devlin B. Common genetic variants, acting additively, are a major source of risk for autism. *Mol Autism*. 2012; 3(1):9. [PubMed: 23067556]

- Lam KS, Aman MG. The Repetitive Behavior Scale-Revised: independent validation in individuals with autism spectrum disorders. *J Autism Dev Disord*. 2007; 37(5):855–866. [PubMed: 17048092]
- Lord, C., Rutter, M., DiLavore, PC., Risi, S. Autism Diagnostic Observation Schedule (ADOS). Los Angeles, CA: Western Psychological Services; 2002.
- Marshall CR, Noor A, Vincent JB, Lionel AC, Feuk L, Skaug J, Shago M, Moessner R, Pinto D, Ren Y, Thiruvahindrapuram B, Fiebig A, Schreiber S, Friedman J, Ketelaars CE, Vos YJ, Ficicioglu C, Kirkpatrick S, Nicolson R, Sloman L, Summers A, Gibbons CA, Teebi A, Chitayat D, Weksberg R, Thompson A, Vardy C, Crosbie V, Luscombe S, Baatjes R, Zwaigenbaum L, Roberts W, Fernandez B, Szatmari P, Scherer SW. Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet*. 2008; 82(2):477–488. [PubMed: 18252227]
- Owley T, Brune CW, Salt J, Walton L, Guter S, Ayuyao N, Gibbons RD, Leventhal BL, Cook EH. A pharmacogenetic study of escitalopram in autism spectrum disorders. *Autism Research*. 2010; 3(1):1–7. [PubMed: 20020537]
- Partington MW, Fagan K, Soubjaki V, Turner G. Translocations involving 4p16.3 in three families: deletion causing the Pitt-Rogers-Danks syndrome and duplication resulting in a new overgrowth syndrome. *J Med Genet*. 1997; 34(9):719–728. [PubMed: 9321756]
- Pinto D, Delaby E, Merico D, Barbosa M, Merikangas A, Klei L, Thiruvahindrapuram B, Xu X, Ziman R, Wang Z, Vorstman JA, Thompson A, Regan R, Pilorge M, Pellicchia G, Pagnamenta AT, Oliveira B, Marshall CR, Magalhaes TR, Lowe JK, Howe JL, Griswold AJ, Gilbert J, Duketis E, Dombroski BA, De Jonge MV, Cuccaro M, Crawford EL, Correia CT, Conroy J, Conceicao IC, Chiocchetti AG, Casey JP, Cai G, Cabrol C, Bolshakova N, Bacchelli E, Anney R, Gallinger S, Cotterchio M, Casey G, Zwaigenbaum L, Wittemeyer K, Wing K, Wallace S, van Engeland H, Tryfon A, Thomson S, Soorya L, Roge B, Roberts W, Poustka F, Mouga S, Minshew N, McInnes LA, McGrew SG, Lord C, Leboyer M, Le Couteur AS, Kolevzon A, Jimenez Gonzalez P, Jacob S, Holt R, Guter S, Green J, Green A, Gillberg C, Fernandez BA, Duque F, Delorme R, Dawson G, Chaste P, Cafe C, Brennan S, Bourgeron T, Bolton PF, Bolte S, Bernier R, Baird G, Bailey AJ, Anagnostou E, Almeida J, Wijsman EM, Vieland VJ, Vicente AM, Schellenberg GD, Pericak-Vance M, Paterson AD, Parr JR, Oliveira G, Nurnberger JI, Monaco AP, Maestrini E, Klauck SM, Hakonarson H, Haines JL, Geschwind DH, Freitag CM, Folstein SE, Ennis S, Coon H, Battaglia A, Szatmari P, Sutcliffe JS, Hallmayer J, Gill M, Cook EH, Buxbaum JD, Devlin B, Gallagher L, Betancur C, Scherer SW. Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. *Am J Hum Genet*. 2014; 94(5):677–694. [PubMed: 24768552]
- Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, Conroy J, Magalhaes TR, Correia C, Abrahams BS, Almeida J, Bacchelli E, Bader GD, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Bolte S, Bolton PF, Bourgeron T, Brennan S, Brian J, Bryson SE, Carson AR, Casallo G, Casey J, Chung BH, Cochrane L, Corsello C, Crawford EL, Crossett A, Cytrynbaum C, Dawson G, de Jonge M, Delorme R, Drmic I, Duketis E, Duque F, Estes A, Farrar P, Fernandez BA, Folstein SE, Fombonne E, Freitag CM, Gilbert J, Gillberg C, Glessner JT, Goldberg J, Green A, Green J, Guter SJ, Hakonarson H, Heron EA, Hill M, Holt R, Howe JL, Hughes G, Hus V, Igliozzi R, Kim C, Klauck SM, Kolevzon A, Korvatska O, Kustanovich V, Lajonchere CM, Lamb JA, Laskawiec M, Leboyer M, Le Couteur A, Leventhal BL, Lionel AC, Liu XQ, Lord C, Lotspeich L, Lund SC, Maestrini E, Mahoney W, Mantoulan C, Marshall CR, McConachie H, McDougle CJ, McGrath J, McMahon WM, Merikangas A, Migita O, Minshew NJ, Mirza GK, Munson J, Nelson SF, Noakes C, Noor A, Nygren G, Oliveira G, Papanikolaou K, Parr JR, Parrini B, Paton T, Pickles A, Pilorge M, Piven J, Ponting CP, Posey DJ, Poustka A, Poustka F, Prasad A, Ragoussis J, Renshaw K, Rickaby J, Roberts W, Roeder K, Roge B, Rutter ML, Bierut LJ, Rice JP, Salt J, Sansom K, Sato D, Segurado R, Sequeira AF, Senman L, Shah N, Sheffield VC, Soorya L, Sousa I, Stein O, Sykes N, Stoppioni V, Strawbridge C, Tancredi R, Tansey K, Thiruvahindrapuram B, Thompson AP, Thomson S, Tryfon A, Tsiantis J, Van Engeland H, Vincent JB, Volkmar F, Wallace S, Wang K, Wang Z, Wassink TH, Webber C, Weksberg R, Wing K, Wittemeyer K, Wood S, Wu J, Yaspan BL, Zurawiecki D, Zwaigenbaum L, Buxbaum JD, Cantor RM, Cook EH, Coon H, Cuccaro ML, Devlin B, Ennis S, Gallagher L, Geschwind DH, Gill M, Haines JL, Hallmayer J, Miller J, Monaco AP, Nurnberger JI Jr, Paterson AD, Pericak-Vance MA, Schellenberg GD, Szatmari P, Vicente AM, Vieland VJ, Wijsman EM, Scherer SW, Sutcliffe JS, Betancur C. Functional impact of global rare copy number variation in autism spectrum disorders. *Nature*. 2010; 466(7304):368–372. [PubMed: 20531469]

- Raven, J. Coloured Progressive Matrices—sets A, A_B, B. Oxford: Oxford Psychologists; 1993.
- Romorini S, Piccoli G, Jiang M, Grossano P, Tonna N, Passafaro M, Zhang M, Sala C. A functional role of postsynaptic density-95-guanylate kinase-associated protein complex in regulating Shank assembly and stability to synapses. *J Neurosci*. 2004; 24(42):9391–9404. [PubMed: 15496675]
- Rutter, M., Le Couteur, A., Lord, C. Autism Diagnostic Interview, Revised (ADI-R). Los Angeles, CA: Western Psychological Services; 2003.
- Sanders SJ, Ercan-Sencicek AG, Hus V, Luo R, Murtha MT, Moreno-De-Luca D, Chu SH, Moreau MP, Gupta AR, Thomson SA, Mason CE, Bilguvar K, Celestino-Soper PB, Choi M, Crawford EL, Davis L, Wright NR, Dhodapkar RM, DiCola M, DiLullo NM, Fernandez TV, Fielding-Singh V, Fishman DO, Frahm S, Garagaloyan R, Goh GS, Kammela S, Klei L, Lowe JK, Lund SC, McGrew AD, Meyer KA, Moffat WJ, Murdoch JD, O'Roak BJ, Ober GT, Pottenger RS, Raubeson MJ, Song Y, Wang Q, Yaspan BL, Yu TW, Yurkiewicz IR, Beaudet AL, Cantor RM, Curland M, Grice DE, Gunel M, Lifton RP, Mane SM, Martin DM, Shaw CA, Sheldon M, Tischfield JA, Walsh CA, Morrow EM, Ledbetter DH, Fombonne E, Lord C, Martin CL, Brooks AI, Sutcliffe JS, Cook EH Jr, Geschwind D, Roeder K, Devlin B, State MW. Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. *Neuron*. 2011; 70(5):863–885. [PubMed: 21658581]
- Shen Y, Dies KA, Holm IA, Bridgemohan C, Sobeih MM, Caronna EB, Miller KJ, Frazier JA, Silverstein I, Picker J, Weissman L, Raffalli P, Jeste S, Demmer LA, Peters HK, Brewster SJ, Kowalczyk SJ, Rosen-Sheidley B, McGowan C, Duda AW 3rd, Lincoln SA, Lowe KR, Schonwald A, Robbins M, Hisama F, Wolff R, Becker R, Nasir R, Urion DK, Milunsky JM, Rappaport L, Gusella JF, Walsh CA, Wu BL, Miller DT. Autism Consortium Clinical Genetics DNADC. Clinical genetic testing for patients with autism spectrum disorders. *Pediatrics*. 2010; 125(4):e727–735. [PubMed: 20231187]
- Skrlec I, Wagner J, Pubelji S, Heffer M, Stipoljev F. De novo case of a partial trisomy 4p and a partial monosomy 8p. *Coll Antropol*. 2014; 38(1):319–323. [PubMed: 24851635]
- Sparrow, SS., Cicchetti, DV., Balla, DA. Vineland Adaptive Behavior Scales, Second Edition (VABS-II). Bloomington, MN: Pearson Assessments; 2005.
- Stilp RL, Gernsbacher MA, Schweigert EK, Arneson CL, Goldsmith HH. Genetic variance for autism screening items in an unselected sample of toddler-age twins. *J Am Acad Child Adolesc Psychiatry*. 2010; 49(3):267–276. [PubMed: 20410716]
- Tranebjaerg L, Petersen A, Hove K, Rehder H, Mikkelsen M. Clinical and cytogenetic studies in a large (4;8) translocation family with pre- and postnatal Wolf syndrome. *Ann Genet*. 1984; 27(4):224–229. [PubMed: 6335368]
- Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding JD, Feliciano C, Chen M, Adams JP, Luo J, Dudek SM, Weinberg RJ, Calakos N, Wetsel WC, Feng G. Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature*. 2007; 448(7156):894–900. [PubMed: 17713528]
- Zuchner S, Wendland JR, Ashley-Koch AE, Collins AL, Tran-Viet KN, Quinn K, Timpano KC, Cuccaro ML, Pericak-Vance MA, Steffens DC, Krishnan KR, Feng G, Murphy DL. Multiple rare SAPAP3 missense variants in trichotillomania and OCD. *Mol Psychiatry*. 2009; 14(1):6–9. [PubMed: 19096451]

Representative images for interphase FISH: **Figure 1.**

Representative interphase FISH images confirmed microarray data of *de novo* 4p duplication and 8p deletion. Two probes were developed for the chr4:53,403-9,016,339=8,962,937 duplication: RP11-69L7 (4p16.3, chr4:752,790-906,783) – SpectrumOrange and RP11-117J13 (4p16.1, chr4: 8,151,525-8,315,477) – SpectrumGreen; and one probe was developed for the chr8:154,984-6,994,825=6,839,842 deletion: RP11-11P7 (8p23.2, chr8:2,612,348-2,798,932) –Biotin (yellow).

D4S394: the proband has three alleles, one paternal allele, and two maternal alleles

Figure 2.

Microsatellite testing of D4S394 revealed two alleles transmitted from the mother (202 and 210, with the 210 peak filled in blue on the proband's electropherogram panel) and one allele transmitted from the father (206) representing a 202/206/210 peak pattern. Because of the leading stutter peak of the father's 206 allele and the trailing stutter peak of the mother's 210 allele, the proband's 204/210 alleles have a similar morphology as the heterozygous 204/210 sibling who did not inherit the mother's 202 allele.

Figure 3.

Microsatellite testing of D8S264 revealed neither of the two 133 alleles of the mother were transmitted to the probands and only the 141 allele from the 141/145 heterozygous father was transmitted to the proband. The unaffected sibling received a 133 allele from the mother and a 145 allele from the father. (This marker had considerable stutter for all alleles which were consistent across subjects.)